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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,302	09/23/2004	Weichang Zhou	21069P	3668

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EXAMINER

CHEN, STACY BROWN

ART UNIT PAPER NUMBER

1648

DATE MAILED: 11/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/509,302

Applicant(s)

ZHOU ET AL.

Examiner

Stacy B. Chen

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 03 August 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-46 is/are pending in the application.
- 4a) Of the above claim(s) 31-46 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-30 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 23 September 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>2/9/06</u> . | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

Applicant's election without traverse of Group I, claims 1-30, is acknowledged. Claims 31-46 are withdrawn from consideration, being drawn to non-elected subject matter. Claims 1-30 are under examination.

#### ***Claims Summary***

The claims are drawn to a method of large-scale virus production, specifically, adenovirus production. The method steps are:

- a. Inoculate a cell growth medium with a population of host cells, wherein the medium contains a shear-protective compound;
- b. Culture the host cells;
- c. Infect the host cells with an aliquot of a virus seed stock essentially free of any cell-lysing component;
- d. Culture the virus-infected host cells under gas sparging;
- e. Harvest intracellular and extracellular virus from the host cells and medium; and,
- f. Purify the harvested virus.

Specifically, the shear-protective compound is selected from the group consisting of Pluronic® F-68, other Pluronic® copolymers, hydroxyethyl starch, derivative of cellulose, serum, tryptosephosphate, polyvinyl alcohol (PVA), bovine serum albumin, polyethylene glycol (PEG) and dextran. In embodiments wherein the shear-protective compound is Pluronic® F-68, the concentration is from about 0.3 g/L to about 10 g/L. During the virus production method, gas sparging is provided at a rate corresponding to a rate up to about 0.1 VVM, or more specifically, a rate up to about 0.001 to 0.05 VVM.

### ***Specification***

The use of the trademark Pluronic® has been noted throughout this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

### ***Claim Objections***

Claims 4-15 and 19-30 are objected to for the following minor informalities:

- ❖ Claims 4 and 19, and dependent claims recite, “wherein Pluronic® F-68 is present at a concentration from about 0.3 g/L and to about 10 g/L.” It appear that the concentration should be “from about 0.3 g/L to about 10 g/L.” Correction is required.
- ❖ Claims 6-15 and 21-30 recite, “a rate corresponding to a rate up to about 0.1 VVM”, and, “a rate corresponding to a rate up to about 0.001 to 0.05 VVM”, respectively. Rates that correspond to other rates appear to be redundant. The Office interprets these phrases as, “a rate up to about 0.1 VVM”, and, “a rate up to about 0.001 to 0.05 VVM”, respectively. Clarification and/or correction is required.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 2-5, 8-15, 17-20 and 23-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the claims contain the trademark/trade name Pluronic® F-68. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a nonionic polymer, and, accordingly, the identification/description is indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 16, 17 and 21-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of large scale virus production described in the claims wherein the shear-protective compound is Pluronic® F-68, does not reasonably provide enablement for any other Pluronic® copolymers, hydroxyethyl starch, derivative of cellulose, serum, tryptosephosphate, polyvinyl alcohol (PVA), bovine serum albumin, polyethylene glycol (PEG) or dextran. The specification does not enable any person skilled in

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the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The breadth of the claims encompasses the large scale production of viruses wherein an effective amount of a shear-protective compound protects virally-infected cells from the effects of gas sparging.

The nature of the invention is the production of viruses via cell culture in large volumes wherein gas sparging is used to provide adequate oxygen and other environmental factors that assist in cell culture and ultimately virus yield.

The prior art demonstrates that baculovirus production in insect cells in the presence of the compound Pluronic® F-68 under gas sparging conditions results in the protection of virally-infected cells. Murhammer *et al.* (*Bio/Technology*, December 1998, 6:1411-1418) discloses that although 0.2% Pluronic® F-68 provided full protection from sparging during growth phase, a higher concentration of Pluronic® F-68 may be required in order to fully protect virally-infected cells (page 1414, first full paragraph). Applicant's own work demonstrates that adenovirus-infected PER.C6™ cells were grown under gas sparging conditions in the presence of Pluronic® F-68 (Xie *et al.*, *Biotechnology and Bioengineering*, July 5, 2003, 83(1):45-52).

The specification provides guidance on the production of replication defective adenoviruses in the presence of Pluronic® F-68 under gas sparging conditions, however, shear-protective components have not been demonstrated as protective of virally-infected cells. As taught by Xie *et al.*, "virus-infected cells behave very differently from uninfected cells under sparging conditions", abstract. Therefore, data regarding the shear-protective properties

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of any other Pluronic® copolymers, hydroxyethyl starch, derivative of cellulose, serum, trptosephosphate, polyvinyl alcohol (PVA), bovine serum albumin, polyethylene glycol (PEG) or dextran for non-infected cells, does not directly translate into an expectation of success for virally-infected cells.

Given the breadth of the claims, the nature of the invention, the state of the art, and the limited guidance and working examples in the specification, the claims are not enabled for their entire scope. Limiting the claims to embodiments wherein the shear-protective agent is Pluronic® F-68 would overcome this rejection.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Murhammer *et al.* (*Bio/Technology*, December 1998, 6:1411-1418, “Murhammer”). The claims are summarized above. Murhammer discloses the scaleup of insect cell cultures using Pluronic® F-68 as a protective agent against cell lysis (abstract). Murhammer extended the study to include the scaleup of insect cell cultures infected with baculovirus comprising a gene encoding  $\beta$ -galactosidase. The following method steps are disclosed in the reference:

- Sf9 insect cells were cultured in spinner flasks to provide cells for seeding the spinner flasks and bioreactors (page 1414, last paragraph). TNM-FH medium was

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supplemented with gentamycin sulfate, Fungizone, heat-inactivated FBS, various concentrations of Pluronic® F-68 (0.2%) and an antifoam compound (see Table 2). Murhammer discloses that although 0.2% Pluronic® F-68 provided full protection from sparging during growth phrase, a higher concentration of Pluronic® F-68 may be required in order to fully protect virally-infected cells (page 1414, first full paragraph).

- Cells were infected with an AcNPV vector containing the *E. coli*  $\beta$ -galactosidase gene (page 1414, last paragraph).
- Infected cells were cultured in a 3-liter water-jacketed bioreactor with a sparger of 7 holes (page 1418, first column, third full paragraph). The sparged reactor was operated at 200 rpm.  $\beta$ -galactosidase synthesis and extracellular virus per  $10^6$  virally-infected cells in sparged and unsparged systems was measured (Table 2 and page 1418, first column, last paragraph, "Quantitation of virus and  $\beta$ -galactosidase activity").
- The extracellular virus was quantified by collecting the supernatant after centrifuging the cell-virus suspension.
- Murhammer quantified virus titers in PFUs/ml using the TCID<sub>50</sub> method.

Given these method steps, Murhammer's method anticipates the claimed invention as described above.

### ***Conclusion***

No claim is allowed.



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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

*Stacy B. Chen* 10/27/06  
STACY B. CHEN  
PRIMARY EXAMINER